REMARKS

Reconsideration of this application is respectfully requested.

Claims 27-47 are presented for further examination. No claims have been amended, added or cancelled by this Amendment.

The title of the invention has been changed to reflect more appropriately the nature of the claimed subject matter. The instant specification has also been amended in two instances above as follows. First, in order to claim priority under the provisions of 35 U.S.C. §120 and to confirm for the record the January 23, 1983 effective filing date of the instant application, information concerning the prior applications in the family has been inserted into the specification (page 1). Second, the language from original claim 1 filed in the seminal great-great-grandparent application (U.S. Patent Application Serial No. 07/461,469) has been appropriately inserted in the summary section of the specification. Originally filed claim 1 was directed to "a substrate having fixed thereto a double-stranded polynucleotide, one of the strands of said double-stranded polynucleotide being a non-radioactive chemically labeled polynucleotide or comprises a non-radioactive chemically-labeled nucleotide as a nucleotide component of said one strand." The preceding language has been inserted into the specification to reflect the language of the present claims which are likewise directed *inter alia* to a double-stranded oligonucleotide or polynucleotide.

Legal precedent for the last-described amendment to the specification is drawn from various sources, including Title 37 Code of Federal Regulations [37 C.F.R. §§1.117 Amendment and revision required. and 1.118 Amendment of Disclosure]; Manual of Patent Examining Procedure (MPEP), §608.04 New Matter; as well as various legal precedents, including, among others, In re Benno, 768 F.2d 1340, 226 USPQ 683 (Fed. Cir. 1985).

§1.117 in Title 37 reads as follows:

> The specification, claims and drawing must be amended and revised when required, to correct inaccuracies of description and definition or unnecessary prolixity, and to secure correspondence between the claims, the specification and the drawing.

With respect to 37 C.F.R. §1.118 Amendment of Disclosure, subsection (a) reads as follows:

> No amendment shall introduce new matter into the disclosure of an application after the filing date of the application (§1.53(b)). All amendments to the specification, including the claims, and the drawings filed after the filing date of the application **must conform to at least one of them as it was at the time of the filing of the application**. Matter not found in either, involving a departure from or an addition to the original disclosure, cannot be added to the application after its filing date even though supported by an oath or declaration in accordance with §1.63 or §1.67 filed after the filing date of the application. [emphasis added]

This rule of practice is also repeated in the MPEP §608.04 New Matter, page 600-62 (Rev. 8, May 1988). Immediately after the recitation of 37 C.F.R. §1.118, the reader is advised:

> In establishing a disclosure applicant may rely not only on the specification and drawing as filed but also on the original claims if their content justifies it. Note >MPEP< §608.01(l).

MPEP §608.01(l) referred to above reads, in turn, as follows:

> **608.01(l) Original Claims**
>
> In establishing a disclosure, applicant may rely not only on the description and drawing as filed but also on the **original claims** if their content justifies it.
>
> Where subject matter not shown in the drawing or described in the description is claimed in the case as filed, and such original claim itself constitutes a clear disclosure of this subject matter, then the claim should be treated on the merits, and requirement made to amend the drawing and description to show this subject matter. The claim should not be attacked either by objection or rejection because this subject matter is lacking in the drawing and description. It is the drawing and description that are defective; not the claim.
>
> It is of course to be understood that this disclosure in the claim must be sufficiently specific and detailed to support the necessary amendment of the drawing and description.
>
> [emphasis added]

In the aforementioned In re Benno case, the Court of Customs and Patent Appeals noted:

> . . . While it is true, as the Solicitor suggested at oral argument, that "a claim is part of the disclosure," that point is of significance principally in the situation where a patent application as filed contains a claim which specifically discloses something not disclosed in the descriptive part of the specification (claims being technically part of the "specification," 35 U.S.C. 112, 2d par.), in which case the applicant may amend the specification without being charged with adding "new matter," within the meaning of §132. See 37 CFR 1.118. ("All amendments to the specification, including the claims, and the drawings filed after the filing date of the application *must conform to at least one of them* as it was at the time of filing the application. . . ." [emphasis in original]

It is submitted that the insertion of the language from the originally filed claim 1 to the specification serves to secure correspondence between the instant claims and the specification, as set forth under 37 C.F.R. §1.117. Such insertion fully and literally complies with the rules of practice, therefore, and no new matter has been inserted thereby.

Applicants and their undersigned attorney appreciate that the indefiniteness rejection (35 U.S.C. §112, second paragraph) from the previous October 22, 1993 Office Action has been withdrawn, and that the double patenting (obviousness-type) rejection will be withdrawn pending review and acceptance of the instant assignee's Terminal Disclaimer submitted with their April 22, 1994 Amendment Under 37 C.F.R. §1.115.

Applicants also note the Examiner's remarks on page 2 of the instant Office Action indicating that several references from their June 2, 1994 Information Disclosure Statement Under 37 C.F.R. §§1.56 & 1.99 were not considered because a copy of the references were not supplied. Although some of the documents not supplied with their June 2, 1994 IDS may have been furnished in some other form (English language equivalent, e.g., a corresponding English language patent document or English abstract), Applicants are nevertheless submitting a copy of each of the documents in question in order to afford the Examiner an opportunity to review them.[1] The documents in question and submitted herewith include the following:

1. DE 2 915 082 (October 31, 1979) {Exhibit 1}; /
   - A. computer search results for family of patents for DE 2 915 082 and English abstract {Exhibit A};
   - B. Kourilsky et al., U.S. Patent No. 4,581,333 {Exhibit B};

[1]The copies of Kourilsky et al. (Exhibit B) and Avrameas et al. below (Exhibit 2) are also believed to be of much better quality and, therefore, more legible than the previously submitted documents.

and

2. Avrameas et al., "Enzyme immunoassay for the measurement of antigens using peroxidase conjugates," Biochemie 54:837-842 (1972) {Exhibit 2}.

With respect to the first above-listed document, DE 2 915 082 (Exhibit 1), it should be noted that the results of a short computer search and English abstract for other language equivalents in the family of patents for this document was also included as Exhibit 41 in Applicants' June 2, 1994 IDS. For the Examiner's convenience, a copy of the search results and English abstract are also submitted herewith as Exhibit A. Listed in Exhibit A among the family is Kourilsky et al., U.S. Patent No. 4,581,333 (highlighted in yellow) that was also submitted as Exhibit 28 in the June 2, 1994 IDS (and is also submitted herewith as Exhibit B). Thus, it would appear to be entirely appropriate and reasonable for the Examiner to rely on the contents of the Kourilsky '333 U.S. patent and the English abstract (Exhibits A and B, respectively) in reviewing the German document, DE 2 915 082 (Exhibit 1). Accordingly, a Form PTO-1449 for DE 2 915 082 is also attached herewith as Exhibit 3 for completion by the Examiner should he consider the other documents (English abstract and related U.S. Patent No. 4,581,333, the latter listed on the Form PTO-1449 along with Avrameas et al.) to be adequate for review and consideration purposes. Applicants and their attorney are hopeful that the foregoing remarks and attached exhibits will satisfactorily clarify the matter of the missing documents or documents not otherwise considered by the Examiner.

Acknowledgement is also made that the Leary et al. document ["Rapid and sensitive colorimetric method for visualizing biotin labeled DNA probes hybridized to DNA or RNA immobilized on nitrocellulose:Bio-blots," Proc. Natl. Acad. Sci (USA) 80:4045-4385 (July 1983)] was also crossed out and/or not considered by the Examiner. The Leary document had been submitted as Exhibit 40 in the June 2, 1994 IDS. Based upon the information on the front page, the publication date of the Leary document is after the January 27, 1983 priority filing date of the first-filed application (Serial No. 06/461,969) in this family. The National Academy of Sciences in Washington, D.C. has confirmed in writing that the publication date for the volume containing the Leary document was July 1, 1983. To complete the record, a copy of the Academy's August 5, 1994 facsimile is attached hereto as Exhibit 4.

Applicants respectfully request that the Examiner consider the above-submitted documents as any of them may relate to the instant application.

Because of their relatively large number (22 in all) and further to faciliate review, it is noted that the following exhibits are attached to this Amendment:

Exhibit No.	Description
1	DE 2 915 082
A	Computer search results & English abstract
B	Kourilsky et al., U.S. Pat. No. 4,581,333
2	Avrameas et al. (1972)
3	Form PTO-1449
4	Natl. Acad. Sci. August 5, 1994 letter
5	Cross v. Iizuka (Fed. Cir. 1985)
6	Brenner v. Manson (S. Ct. 1966)
7	Enzo Diagnostics, Inc. 1992 Product Catalog
8	HIV Product Description Sheet
9	Rapier et al. (1993)
10	In re Langer (C.C.P.A. 1974)
11	Declaration In Support of Utility of Dr. Dean L. Engelhardt
I	Engelhardt et al., U.S. Pat. No. 5,241,060 (attached to Engelhardt Declaration)
12	Milliman et al., U.S. Pat. No. 5,232,831
13	Innis, U.S. Pat. No. 5,142,033
14	Rogers et al., U.S. Pat. No. 5,134,066
15	Bodmer et al., U.S. Pat. No. 5,098,823
16	Ellis et al., U.S. Pat. No. 4,960,690
17	Dattagupta et al., U.S. Pat. No. 4,724,202
18	Ward et al., U.S. Pat. No. 4,711,955
19	Stephenson et al., U.S. Pat. No. 4,681,840
20	3/3/92 Office Action (Milliman '831 patent)
21	Milliman's Response to 3/3/92 Office Action
and 22	8/6/92 Office Action (Milliman '831 patent).

THE REJECTION UNDER 35 U.S.C. §101

Claims 27-45 stand finally rejected under 35 U.S.C. §101 for lack of utility. This is the sole remaining rejection in the application except for the double patenting rejection which is pending review and acceptance of the assignee's Terminal (Statutory) Disclaimer. In the Office Action (pages 2 and 3), the Examiner stated that "there is no instantly disclosed utility for a double stranded containing composition. This rejection is reiterated and maintained as set forth in the previous office action mailed 10/22/93. Applicants argue that the double-stranded form is an intermediate prior to detection. This is non-persuasive in that this utility has not been found in the disclosure as filed. Adding it at this time does not support the utility of the invention as disclosed. Also applicants argue that double-stranded form passes the strictures of utility irrespective of whether detection has been carried out. This is confusing and non-persuasive because the Examiner is unaware of an inherent utility in double-stranded nucleic acid."

In the prior October 26, 1993 Office Action, then-pending claims 27-45 were rejected under 35 U.S.C. §101 "because there is no instantly disclosed utility for a double stranded containing composition. It is acknowledged that probes that are single stranded have utility as probes but after a double stranded form has been produced as cited in claims 27-45, it no longer has a utility as for detection."

The rejection for lack of utility is respectfully traversed.

In response, Applicants respectfully submit that the utility of the instant invention is well established on several grounds.

The Legal Test For Utility

The legal test for utility was well stated by the Court of Appeals for the Federal Circuit (CAFC) in the 1985 case of Cross v. Iizuka [753 F.2d 1040, 224 USPQ 739 (Fed Cir. 1985)]. A copy of the Cross case is attached hereto as Exhibit 5. Although involving an interference, the Federal Circuit properly enunciated the legal test for utility:

> Proper resolution of the issues before this court necessitates that we address, seriatim, the following questions: (1) What utility is disclosed by the Japanese priority application? (2) Does this stated utility comply with the "practical utility" requirement of 35 U.S.C. §101, as delimited by prior decisions of the judiciary?[8] . . .
>
> It is axiomatic that an application cannot be considered "useful," in the sense that a patent can be granted on it, unless substantial or practical utility for the invention has been discovered and disclosed where such utility would not be obvious. Brenner v. Manson, 383 U.S. 519, 148 USPQ 689 (1966). . .

In footnote 8 the Court elaborated on the two questions stated above:

> While questions one and two are closely connected, a thorough analysis of the utility issue requires first, a determination as to what utility is disclosed, i.e., the stated utility, for the invention claimed in the application. Only after the stated utility has been determined, can a proper analysis be undertaken to determine if the stated utility complies with the "practical utility" requirement of §101. As noted above, these questions regarding utility are factual in nature, see supra note 7, and are to be determined in the first instance by the PTO, the agency with the expertise in this regard.

Footnote 7 referenced above states:

> Utility is a fact question. Raytheon Co. v. Roper Corp., 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983), cert. denied, 105 S. Ct. 127 (1984). Enablement under §112, paragraph 1, i.e., the how-to-use requirement, is a question of law. Id. at 960 n. 6, 220 USPQ at 599 n. 6.

In effect, the legal standard for utility requires **first**, that the instant invention meet its utility stated in the disclosure (unless such utility is obvious; see Cross v. Iizuka, *supra*), and **second**, that the invention achieve a "practical" utility as promulgated by the courts. Practical utility means that the utility must be definite and in currently available form and not merely for further investigation or research but commercial availability is not necessary. See, e.g., Brenner v. Manson, 383 U.S. 519, 148 USPQ 689 (S. Ct. 1966), a copy of which is attached as Exhibit 6.

(I) Applicants' Inventi n Clearly Meets Its Stated Utilities

(A) Qualitative Determination of Nucleic Acid or Genetic Material

In their April 22, 1994 Amendment (see page 4, last paragraph, through page 5, first paragraph), Applicants had indicated that:

> . . . the double-stranded oligonucleotide or polynucleotide recited in the instant claims does indeed possess utility in that the actual detection of the polynucleotide sequence of interest may not have been carried out at the point where the double-stranded form has been produced. In effect, in the instant invention, Applicants are claiming an intermediate product which can be detected. The changes to the signalling moiety in claims 27 and 47, which conform to the issued claims in U.S. Patent No. 4,994,373, reflect this aspect. It is further respectfully submitted that such a "double stranded form" as set forth in the instant claims, pass the statutory strictures for utility, irrespective of whether detection has been carried out.

Applicants respectfully maintain their above-stated position with respect to the instant composition possessing the aforementioned utility as an intermediate.

Applicants further wish to point out that the disclosure as-filed clearly and expressly establishes the utility of the instantly claimed invention, (e.g., claim 27), i.e., a double-stranded oligonucleotide or polynucleotide . . wherein one of the the strands comprises a chemical label that further comprises a signalling moiety which is capable of generating a soluble signal. In fact, the original as-filed disclosure is replete with information directed to the utility of the instant invention as described in full detail below.

For example, Applicants state in the "SUMMARY OF THE INVENTION (page 21, line 17, through page 22, line 10):

> In accordance with the practice of this invention, non-radioactive chemically labeled polynucleotides are prepared such as non-radioactive chemically labeled single-stranded DNA probes. Such probes are then brought into contact with genetic material to be identified or otherwise detected. Before these probes are brought into contact with the genetic material to be identified or investigated, the genetic material

> is denatured to produce or form single-stranded genetic material therefrom, such as single-stranded DNA derived from the genetic material. Desirably, the resulting single-stranded genetic material is fixed to a suitable inert support or surface such as a plastic material, e.g. polystyrene, preferably a transparent or translucent surface such as glass. Thereupon, the special non-radioactive chemically-labeled probes, such as the special non-radioactive chemically-labeled single-stranded DNA probes of this are brought into contact with the thus-fixed single-stranded genetic material under hybridizing conditions. The probe is selected to provide sufficient number, e.g. at least about 25 bases, in its make up, complementary to the bases making up the genetic material to be detected or identified. The hybridization of the probe to the singlestranded(sic) genetic material to be identified with resulting double-stranded or duplex formation **would be then detected** by means of the non-radioactive chemical label attached to the probe portion of the resulting formed doublestranded hybrid or duplex hybrid. [underline & bold added]

Furthermore, beginning on page 22, line 34, and continuing through page 23, line 10, Applicants disclose:

> Spectrophotometric or colorimetric techniques . . . also usefully provide a prompt visual manifestation or elicitation of the non-radioactive chemical label in the resulting formed double-stranded hybrid. Other ELISA-like or related techniques are also useful for the detection of the non-radioactive chemical label in the formed duplex, such other techniques would also involve the use of enzymes, e.g. immunoperoxidase, or the use of electron dense markers, e.g. immunoferritin, or other chemical and/or physical markers, attachable or attached to the probes. Broadly, the practices of this invention provide techniques comparable to enzyme linked immunosorbent assay techniques, not only for the qualitative, but also the quantitative determination of hybrid formation.
>
> [underline added]

In addition, Applicants disclose on page 24 (lines 14-29):

> For example, glass plates provided with an array of depressions or wells therein would have samples of the various denatured genetic materials to be identified deposited therein and the single-stranded DNA material therein fixed to the surfaces of the wells. Thereupon, DNA probes provided with a non-radioactive chemical label are deposited in each of the wells for hybridization to any complementary single-stranded DNA material therein. After washing to remove any non-hybridized probe, the presence of any hybrid DNA material

> containing the single-stranded DNA material to be identified and the non-radioactive chemically-labeled probe is detected, as described herein, involving the addition of an enzyme linked antibody or other suitable entity for attachment to the chemical label of the probe. Subsequently a suitable substrate is added to elicit a color change or chemical reaction which could then be measured colorimetrically or photometrically.
> [underline added]

Thus, the instant composition is clearly useful for the qualitative determination of nucleic acid or genetic material.

(B) Quantitative Determination of Nucleic Acid or Genetic Material

In addition to qualitative analysis, the instant composition is also useful for quantitatively determining a nucleic acid or genetic material of interest - and this utility is also set forth explicitly in the original disclosure.

In lines 10-22 on page 22, Applicants disclose:

> Various techniques, depending upon the non-radioactive chemical label employed in the make up of the probe, may be employed to detect the formation of the double strand or duplex hybrid. It is preferred, however, in the practices of this invention, to employ spectrophotometric techniques and/or enzyme linked immunosorbent assay (ELISA) techniques for the determination of the formed hybrid. Spectrophotometric and ELISA techniques permit not only the detection of the resulting formed double-stranded hybrid, but also permit the quantitative determination thereof, such as by the enzymatic generation of a product that can be measured colorimetrically or fluorometrically. . . . [underline added]

Further in lines 12-20, Applicants state:

> As indicated, it is preferred to use ELISA techniques to effect or bring about the expression or indication of, qualitatively or quantitatively, of the non-radioactive chemically-labeled probe **in the resulting formed double-stranded or hybridized material**, such as the duplex or hybrid formed by the non-radioactive chemically-labeled DNA probe and its substantially complementary genetic DNA material derived from the denatured denetic(sic) DNA material to be identified.
> [underlined & bold added]

In the second paragraph on page 28, Applicants again refer to the quantitative as well as the qualitative utility of the instant composition:

> In the above test employing glucosylated DNA as a probe, wherein the glucosyl or monosaccharide moiety of the glucosylated DNA probe serves as the non-radioactive chemical label, comparable results are also achievable in the practices of this invention employing a biotin-labeled DNA probe. When biotin is employed as the non-radioactive chemical label of the DNA probe, and since avidin is strongly reactive with or strongly binds to biotin, the presence of the biotin-labeled DNA probe would be elicited or detected by means of avidin or streptavidin-labeled enzyme. For example, a biotin-labeled DNA probe would readily be detected by an enzyme complex of the character avidin-biotin-alkaline phosphatase. More specifically, the presence of the biotin-labeled probe with the enzyme complex avidin-biotin-alkaline phosphatase, followed by bringing the resulting biotin-labeled DNA probe having attached thereto the avidin-biotin-alkaline phosphatase complex into contact with a suitable substrate which by color reaction or precipitate formation brought about by the alkaline phosphatase would be readily noticed or capable of being determined, both qualitatively **and quantitatively**, by photometric and/or colorimetric means in accordance with ELISA techniques. If desired, instead of an avidin-biotin-enzyme complex, there could be used an antibody to biotin for attachment to the biotin moiety of the biotin-labeled DNA probe, followed by a complex comprising anti-antibody-enzyme in the manner described hereinabove. [bold added]

Later in the second paragraph on page 30, Applicants elaborate on the quantitative utility of the instant composition:

> Additional tests were carried out wherein several aliquots of denatured adenovirus 2 DNA were bound to polystyrene plates as described above. After blocking with Denhardt's formamide blocking buffer, several biotinylated probes were hybridized to the immobilized DNA; these were B-adeno-2-DNA and lambda DNA. To one set of immobilized DNA, no probe was added. The extent of hybridization was determined by means of the antibody-enzyme reaction as described above. It was observed that only the homologous adeno-2 probe hybridized. This technique demonstrated that <u>in vitro</u> hybridization under these conditions is specific **and can be monitored quantitatively.** [bold added]

Finally, in lines 19-24 on page 32, after referring to Tables I and II found on pages 33 and 34, respectively, Applicants again point to both the qualitative and quantitative aspects of the utility for the instant composition where they disclose:

> . . . These combinations of enzyme-chromogen are particularly useful in ELISA techniques for the determination, both qualitatively and quantitatively, of the hybrid DNA or other genetic material *containing* the special non-radioactive chemically-labeled probe in accordance with this invention.
> [underline and emphasis added]

It is respectfully submitted, therefore, that at least two legally sufficient utilities - qualitative detection and quantitative determination - are explicitly stated in the original disclosure. Moreover, the instant composition clearly meets both stated utilities, and by so doing, meets the first criterion of the utility test set forth in Cross, *supra*.

(II) Applicants' Invention Clearly Meets The Courts' Practical Utility Tests

As set forth in the Cross case, *supra*, after determining that it meets its stated utility, the claimed invention must be further examined in terms of its practical utility. Here, in this instance, Applicants are obliged to point out that the instant composition is usefully employed in the "microplate" assay, a format highly popular in industry and research. Marketed under the tradename, Enzo Microplate Hybridization Assay, the instant assignee, Enzo Diagnostics, Inc. currently sells two products, one for detecting Human Immunodeficiency Virus (HIV) and the other for detecting *Mycobacterium tuberculosis* complex, i.e., members of the MTB complex. Attached hereto as Exhibit 7 is a copy of selected pages from the instant assignee's 1992 Product Catalog, including page 22 which describes the aforementioned HIV and MTB Microplate Hybridization Assay products. In conjunction with the former, Applicants are also submitting as Exhibit 8 a copy of the product description sheet titled "HIV Detection from Enzo Diagnostics - The Enzo Microplate Assay for HIV DNA." This product and methodology was the subject of a 1993 Clinical Chemistry paper [Rapier et al., "Nonradioactive, Colorimetric Microplate Hybridization Assay for Detecting Amplified Human Immunodeficiency Virus DNA," Clinical Chemistry, 39:244-247 (1993)], a copy of which is attached as Exhibit 9.

Based upon the foregoing exhibits (7-9), the instant composition clearly meets and even exceeds the practical utility requirements laid down by the courts. Thus, the instant composition satisfies both prongs of the utility test described in Cross, *supra*.

Other Considerations

1. ***The Instant Invention Is Useful in Carrying Out the Methods in U.S. Patent No. 4,994,373.***

The issued claims in U.S. Patent No. 4,994,373 which was based upon the grandparent application, U.S. Patent Application Serial No. 07/385,986, are directed to a method, device and kit which employ *inter alia* the instantly claimed composition. In claim 1 of U.S. Patent No. 4,994,373, a method is recited in which an entity is formed

> comprising said polynucleotide sequence hybridized to a polynucleotide or oligoncleotide probe, said probe having attached thereto a chemical label further comprising a signalling moiety capable of generating a soluble signal; **and generating and detecting said soluble signal.**
>
> [underlined and bold added]

The instant invention is clearly useful for carrying out the already issued claims in U.S. Patent No. 4,994,373, and as such, the utility of the present claims is *ipso facto* established.

2. ***Applicants' Invention Is Objectively Useful Under the Law.***

As set forth in the opening remarks of this Amendment, Applicants would also like to reiterate that the originally filed claims in the great-great-grandparent application, U.S. Patent Application Serial No. 06/461,469, filed on January 27, 1983, were similarly directed to a double-stranded polynucleotide (see, e.g., original independent claims 1, 19, 68, 73, and the claims dependent therefrom). Thus, the instantly claimed invention does not in any way represent some dramatic new twist or abrupt departure from the original disclosure and claims, it being Applicants' clear and unequivocal intent to claim a double-stranded nucleic acid as a distinct feature of their invention both when the seminal application (Serial No. 06/491,469) was originally filed in 1983 - and now at the present time. Furthermore, the presently claimed subject matter

corresponds in scope to the disclosure of utility in the specification as evidenced by: (1) specific statements of utility in the disclosure (described above; see page 9 through the middle of page 13); and (2) the scope of the originally filed claims, i.e., double-stranded polynucleotide. See, e.g., Manual of Patent Examining Procedure (MPEP), §608.01(l) **Original Claims**. As the Federal Circuit's predecessor court declared in In re Langer [503 F.2d 1380, 183 USPQ 288 (C.C.P.A. 1974)]:

> As a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented *must* be taken as sufficient to satisfy the utility requirement of §101 for the entire claimed subject matter *unless* there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope. Assuming that sufficient reason to question the statement of utility and its scope does exist, a rejection for lack of utility under §101 will be proper on that basis; such a rejection can be overcome by suitable proofs indicating that the statement of utility and its scope as found in the specification are true. (citations omitted)
> [503 F.2d at 1391, 183 USPQ at 297]

A copy of the In re Langer case is attached as Exhibit 10.

In this instance, Applicants respectfully submit that no sufficient reason exists to question the statements of utility in the original disclosure, nor its scope. Moreover, the fact that the instant composition is commercially employed in the instant assignee's microplate hybridization assay (see this Amendment, page 14, last paragraph; and Exhibits 7-9), constitutes more than ample proof that the statements of utility in the original disclosure and their scope are true.

3. ***The utility of the claimed invention is obvious from the original as-filed disclosure.***

In both the Cross, *supra*, and Brenner v. Manson, *supra*, cases, the respective courts noted that an application cannot be considered "useful," in the sense that a patent can be granted on it, unless substantial or practical utility for the invention has been discovered and disclosed where such utility would not be obvious. To put it in other converse terms, to meet the judicially imposed test, substantial or practical utility for a claimed invention must be disclosed or be otherwise obvious.

In this instance, Applicants are firmly of the opinion that the original disclosure clearly sets forth both stated and practical utilities for the presently claimed invention. While not believed to be necessary to the resolution of the utility issue, Applicants are nevertheless submitting herewith as Exhibit 11 the signed Declaration In Support of Utility of Dr. Dean L. Engelhardt, who is Senior Vice President of Enzo Biochem, Inc., the parent company of the instant assignee. Dr. Engelhardt's Declaration is believed to be cumulative evidence on the utility issue for the instant invention. Nevertheless, the Examiner is respectfully invited to consider Dr. Engelhardt's Declaration in any case. Prior to his present position at Enzo, Dr. Engelhardt had been an Associate Professor of Microbiology at Columbia University College of Physicians and Surgeons, New York City, having obtained his doctorate from Rockefeller University in New York City. As set forth in his Declaration (paragraph 3), Dr. Engelhardt is familiar with the contents of this application, the pending claims 27-47, the original disclosure represented by U.S. Patent Application Serial No. 06/491,469 (filed on January 27, 1983), and further, that he has reviewed both the July 25, 1993 Office Action and the earlier October 26, 1993 Office Action issued in connection with the subject application.

As set forth in Paragraph 3 in his Declaration, Dr. Engelhardt also served as Director of Research for Enzo, overseeing scientific research activities and having responsibility for the development of new nucleic acid technology and hybridization formats, including new diagnostic and therapeutic approaches and agents based upon nucleic acid technology. As such, Dr. Engelhardt states that he is quite familiar with the technology relating to this application and the pending claims.[2]

In Paragraph 8 of his Declaration, Dr. Engelhardt states that the instant double-stranded composition is useful in carrying out the assay disclosed in the specification (see, for example, the section in the specification titled "SUMMARY OF THE INVENTION," beginning on page 21, line 15, through page 22, lines 9+) and that the disclosed assay is also the subject of the method claims in related U.S. Patent No. 4,994,373. In Paragraph 9, Dr. Engelhardt describes in detail the utility of the instantly claimed composition. According to Dr. Engelhardt, a double-stranded composition is formed, such as defined in claim 27, where the chemically labelled strand is itself immobilized (see the specification, for example, page 26, second paragraph; and page 29, lines 1-3 and lines 21-24), or

[2]It is respectfully submitted, moreover, that Dr. Englehardt is clearly a person of at least ordinary skill in the art to which the instant invention pertains, based upon his knowledge, formal training, background and professional experience.

where the chemically labelled strand becomes immobilized through its specific recognition of the sequence in the other strand fixed or immobilized to the solid support (see the specification, for example, page 21, line 27, through page 22, line 9; page 27, last paragraph; and page 30, second paragraph). The hybridized signal carrying strand is distinguished from any unhybridized signal carrying strands to provide qualitative detection or quantitative determination of a nucleic acid or genetic material of interest.

In the same paragraph (¶ 9), Dr Engelhardt describes how from the disclosure the hybridized signal carrying strands are distinguished from the unhybridized signal carrying strands. If, for example, the signal carrying strand in solution hybridizes to a strand already fixed or immobilized to a solid support, then an obvious and altogether conventional procedure such as washing is performed to rid the assay system of the single-stranded signal carrying strand in solution (see specification, for example, page 27, last paragraph, particularly lines 29-31). The detection of the soluble signal (the label not washed out) in such an instance is a measure of the soluble signal present in the double-stranded oligo- or polynucleotide. If, on the other hand, for example, the signal carrying strand is itself fixed or immobilized to the solid support, single strands can be conventionally and selectively destroyed through obvious and conventional procedures such as enzymatic digestion using for example, an S1 nuclease, or an S1 nuclease in conjunction with other nucleases, such as, exonuclease I. See, for example, column 20, lines 25-35 in Engelhardt et al., U.S. Patent No. 5,241,060, issued on August 31, 1993 (copy attached to Dr. Engelhardt's Declaration as Exhibit I). The Engelhardt '060 patent issued from an application related to the great-greatgrandparent of the instant application (Serial No. 06/391,440, filed on June 23, 1982). Page 13 (lines 1-3); and page 21 (second paragraph) in the instant specification both refer to the aforementioned Serial No. 06/391,440 and the latter in fact incorporates it by reference into the instant specification. According to Dr. Engelhardt (¶ 9), the remaining label will be a valid measure of the unlabelled strand because the unhybridized single strands (labelled or unlabelled) will have been eliminated, and, therefore, from the double-stranded composition formed intermediately, useful and even crucial functions and analyses can be performed in accordance with the instant disclosure. Dr. Engelhardt states that the aforedescribed utility is obvious from the instant disclosure, and would have been obvious to any person familiar with the technology and subject matter to which the instantly claimed invention pertains.

In the final paragraph (¶ 10) of his Declaration, Dr. Engelhardt declares that in order to perform the assay, a double-stranded composition must be formed if the nucleic acid or genetic material of interest is present. The double strand results from the recognition and hybridization of the two oligonucleotide or polynucleotide strands, one strand being unlabelled and the other comprising a chemical label further comprising a signalling moiety capable of generating a soluble signal. According to Dr. Engelhardt, the double-stranded composition is *sine qua non* in the differentiation between reacted (hybridized) and unreacted (unhybridized) labelled oligonucleotide or polynucleotide. Dr. Engelhardt concludes his Declaration to the effect that the double-stranded oligonucleotide or polynucleotide in the instant composition is useful in carrying out the patented assay method set forth in U.S. Patent No. 4,994,373, and that this utility is obvious from the present disclosure, if not explicitly stated in the specification.

4. ***Past Policy and Practices of The Patent Office Do Not Bar On The Basis of Lack of Utility Under 35 U.S.C. §101 Compositions For Double Stranded Nucleic Acid.***

It should not go unrecognized or be overlooked that The U.S. Patent and Trademark Office has issued several patents with composition claims reciting double-stranded nucleic acid (or equivalent terminology) in the issued claims. Merely to illustrate this point, Applicants respectfully wish to bring to the Examiner's attention the following eight (8) U.S. patents, each one of which issued with at least one claim similar to the language at issue in the instant rejection:

(1) Exhibit	(2) U.S. Patent No.	(3) Exemplary Claims	(4) Recited Terminology
12	5,232,831	**9**	nucleic acid hybrid
13	5,142,033	**1** & 2	a double-stranded DNA
14	5,134,066	**23** & 24-25	nucleic acid duplex
15	5,098,823	**2**	double-stranded DNA fragment

Exhibit	U.S. Patent No.	Exemplary Claims	Recited Terminology
16	4,960,690	**21** & 22-26	double-stranded DNA
17	4,724,202	**49** & 50-51	detection probe comprising a hybridizable double stranded portion of nucleic acid connected to a non-hybridizable, double stranded nucleci acid portion, the non-hybridizable portion modified by a fluorescent moiety
18	4,711,955	**15** & 16-20	double-stranded RNA or DNA duplex or DNA-RNA hybrid
19	4,681,840	**4**	double-stranded deoxyribonucleic acid molecule

As indicated above, a copy of each of the eight patents listed above are attached as Exhibits 12-19, respectively. The numbers in bold in column 3 above refer to independent claims in the patent. As can be easily discerned from the recited terminology listed above for each patent, many claims specifically define double-stranded nucleic acid (or equivalent language, such as duplex or hybrid). Applicants and their attorney are willing to recognize that the disclosures for each patent and patent application are clearly different and unique in their own right, and that broad generalizations regarding prosecution histories should be carefully examined. Having said that, however, a careful review of each of these patents does not reveal that any statements of utility are any more (or for that matter even any less) extraordinary than the statements of utility in the original disclosure at hand. Moreover, in each of these eight (8) patents, a review by Applicants' attorney of the file wrappers (and more particularly, the nineteen (19) or so office actions issued respectively therein) has revealed only one single instance where a rejection was made for lack of utility merely from the fact that a double-stranded nucleic acid (or equivalent terminology) was being claimed.[3] The single instance occurred in the March 3, 1992 Office Action issued in connection with

[3]As previously described in this Amendment, a double-stranded polynucleotide was also the subject of several of the originally filed claims in the priority document, U.S. Patent Application Serial No. 07/461,469. See, e.g., original claims 1, 68 and

Milliman's ultimately issued '831 patent (Exhibit 12). For the Examiner's convenience, a copy of each of the March 3, 1992 Office Action, Milliman's July 6, 1992 Response, and the subsequent August 6, 1992 (final) Office Action, are attached as Exhibits 20, 21 and 22, respectively. A copy of all the remaining seventeen (17) offices actions issued in the other seven patents are available should the Examiner wish to review them.

As set forth on pages 2 and 3 in the March 3, 1992 Office Action (Exhibit 20), the examiner handling the Milliman application rejected two claims (7 and 11) under 35 U.S.C. §101 "because the claimed invention lacks patentable utility. Whereas a single-stranded probe has utility, there is no evident utility for the nucleic acid hybrids claimed in claims 7 and 11 and no utility for the hybrids is disclosed in the specification."

In their July 6, 1992 Response (pages 10 and 11) [Exhibit 21], Milliman et al. argued that their double-stranded hybrids claimed in claims 7 and 11 have patentable utility, supporting their position with the following two paragraphs:

> One example of the utility of the double-stranded hybrids is disclosed in the specification. The specification discloses the use of the double-stranded hybrids in a hybridization protection assay which allows Streptococcus pyrogenes to be distinguished from its known and presumably most closely related taxonomic or phylogenetic neighbors. The assay consists of labelling an oligonucleotide probe that is complementary to rRNA sequences in Streptococcus pyrogenes with a chemiluminescent molecule, an acridinium ester; the labelled probe is then incubated with target rRNA sequences to form stable hybrid molecules, such as those claimed in claims 7 and 11. These stable hybrid molecules are crucial to detection of Streptococcus pyrogenes in such an assay. Labelled double-stranded hybrid molecules are distinguished from labelled single-stranded probe molecules by treating with alkaline borate which hydrolyzes the single-stranded probe. The double-stranded hybrid remains intact after hydrolysis and can be detected by chemiluminescence; therefore the amount of chemiluminescence remaining after hydrolysis is proportional to the amount of hybrid formed and indicates the amount of Streptococcus pyrogenes present in the sample. The hybrid molecules are therefore critical to the invention.

(Footnote 3 Continued) 73. A review of the file histories from the other four (4) prior applications revealed that seven (7) office actions were ultimately issued in the family, and that no rejection of any "double-stranded" type claims was ever made - apart from the instant Office Action and the previous October 26, 1993 Office Action.

> Because of their importance to the detection of Streptococcus pyrogenes in the chemiluminescence hybridization protection assay; the hybrid molecules claimed in claims 7 and 11 satisfy the requirement of utility under 35 U.S.C. §101. Applicant respectfully requests that the rejection of claims 7 and 11 be withdrawn.

Subsequently, in the final August 6, 1992 Office Action (Exhibit 22), the examiner withdrew the utility rejection, indicating that "[a]ll of the objections and rejections made in Paper #11 have been overcome by the amendments and arguments made in Paper #14 filed on 7/9/92."

As evidenced by the eight (8) or so U.S. patents having issued with double-stranded composition claims (Exhibits 12-19), the instant utility rejection is not a case of first impression. It would appear that the past practices of The Patent Office do not in any way preclude on the basis of §101 the claimed subject matter at hand. In fact, the issuance of the several U.S. patents listed above (Exhibits 12-19) and the nineteen (19) office actions collectively gleaned from their respective file wrappers point to what could only be reasonably construed as a tacit acceptance if not open sanctioning of compositions involving double-stranded nucleic acid (or equivalent language) in claims presumed to be valid under the law (35 U.S.C. §282), and even more importantly, useful under 35 U.S.C. §101. In addition, Applicants' attorneys are unaware of any recent statutory or rule change, or judicial interpretation substantively affecting the utility requirements under §101 that would support the instant rejection. If the instant rejection is based upon a recent change in PTO policy, Applicants and their attorneys would appreciate an indication to that effect together with the underlying basis under which the new PTO policy was implemented.

In view of the foregoing remarks, submitted exhibits and established legal principles, Applicants respectfully request reconsideration and withdrawal of the utility rejection, thereby placing all of the present claims, 27-47, in allowable condition.

In order to expedite review, Applicants' attorney is filing this Amendment and the attached twenty-two (22) exhibits by Express Mail, and is also sending by courier a courtesy copy of the Amendment (without exhibits) to Examiner (Dr.) Ardin Marschel, Group Art Unit 1807.

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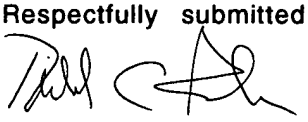
SUMMARY AND CONCLUSIONS

Claims 27-47 are presented for further examination. No claims have been amended, added or cancelled by this Amendment. Further, no new matter has been inserted by any of the amendments to the specification herein.

This Amendment is being timely filed. Therefore, no fee is believed due. In the event, however, that any fee or fees are deemed due, The Patent and Trademark Office is hereby authorized to charge the amount of any such fee(s) to Deposit Account 05-1135, or to credit any overpayment thereto.

In view of the above discussion of the issues and the numerous submitted exhibits, Applicants respectfully submit that each of claims 27-47 is in condition for allowance. A favorable and speedy reconsideration of their rejection is requested. If any of these claims are found not to be in condition for allowance for any reason, the Examiner is respectfully requested to telephone the undersigned at (212) 856-0876 to discuss the subject application.

Respectfully submitted,



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